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(71) Applicant *(for all designated States except US)*: **H. LUNDBECK A/S** [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BECH SOMMER, Michael** [DK/DK]; Aldershvilevej 28A, DK-2880 Bagsværd (DK). **NIELSEN, Ole** [DK/DK]; Nystedvej 19, DK-2500 Valby (DK). **PETERSEN, Hans** [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). **AHMADIAN, Haleh** [DK/DK]; Digeparken 12, DK-2680 Solrød Strand (DK). **PEDERSEN, Henrik** [DK/DK]; Mellemvangen 63, DK-2700 Brønshøj (DK). **BRØSEN, Peter** [DK/DK]; Kanonej 45, DK-2730 Herlev (DK). **GEISER, Fiona** [US/US]; 287 A Wilson Avenue, Glen Mills, PA 19342 (US). **LEE, James** [US/US]; 814 St. Christopher Lane, Philadelphia, PA 19116 (US). **COX, Geoffey** [GB/US]; 1505 Windermere Rd, Apartment 203, West Chester, PA 19380 (US). **DAPREMONT, Olivier** [FR/US]; 1550 Iron Point Road, #221, Folsom, CA 95630 (US). **SUTEU, Christina** [FR/FR]; 14 rue du Lt Homps, F-67400 Illkirch (FR). **ASSENZA, Sebastian, P.** [US/US]; 15 Truxton Lane, Fort Salonga, NY 11768 (US). **HARIHARAN, Shankar** [US/US]; Forest Labs, Inwood, NY (US). **NAIR, Usha** [US/US]; 6337 Willow Oak Drive, Nashville, TN (US).

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(54) Title: METHOD FOR THE PREPARATION OF ESCITALOPRAM

(57) Abstract: A novel method is provided for the manufacture of escitalopram. The method comprises chromatographic separation of the enantiomers of citalopram or an intermediate in the production of citalopram using a chiral stationary phase such as Chiralpak™ AD or Chiralcel™ OD. Novel chiral intermediates for the synthesis of Escitalopram made by said method are also provided.

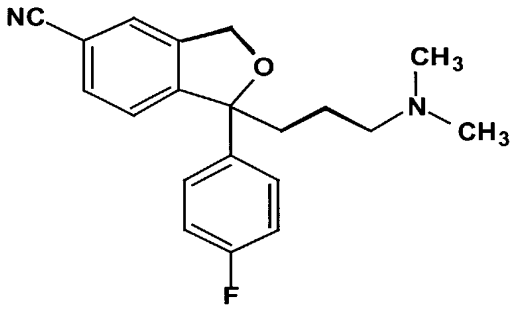
METHOD FOR THE PREPARATION OF ESCITALOPRAM

Field of invention

The present invention relates to the preparation of the compound escitalopram, which is the S-enantiomer of the well-known antidepressant drug citalopram, i.e. (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, or a pharmaceutically acceptable salt thereof for the preparation of pharmaceutical preparations.

Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:

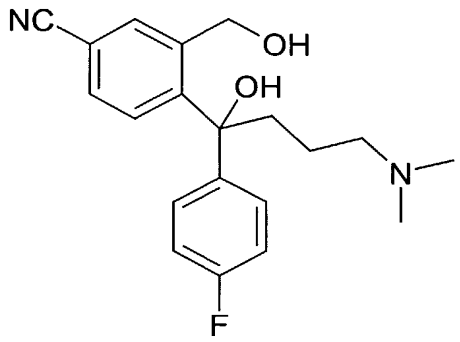


(I)

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication i.a. outlines a process for the preparation of citalopram from the corresponding 5-bromo-derivative by reaction with cuprous cyanide in a suitable solvent. Further processes for the preparation of citalopram by exchange of 5-halogen or CF_3-$(CF_2)_n$-SO_2-O-, n being 0-8, with cyano are disclosed in WO 0011926 and WO 0013648.

The diol of formula II, 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile, and its use as an intermediate in the preparation of citalopram has been disclosed in e.g. US patent No 4,650,884.



(II)

Escitalopram, the enantiomers of the diol II and methods for their preparation are disclosed in US Patent No 4,943,590. Two routes to escitalopram are disclosed, both of them are starting with the racemic diol II. In the first route, the diol II is reacted with an enantiomerically pure acid derivative, such as (+) or (-)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride to form a mixture of diastereomeric esters, which are separated by HPLC or fractional crystallization, whereupon the ester with the right stereochemistry is enantioselectively converted into escitalopram. In the second route, the diol II is separated into the enantiomers by stereoselective crystallization with an enantiomerically pure acid such as (+)-di-p-toluoyltartaric acid, whereupon the S-enantiomer of the diol II is enantioselectively converted to escitalopram. Both of these routes involve consumption of expensive, enantiomerically pure reagents and give relatively low yields resulting in that they are economically and environmentally infeasible for industrial production. The stereoselectivity of the pharmacological action of citalopram, i.e. the 5-HT-reuptake inhibition residing in the S-enantiomer, and accordingly, the antidepressant effect of said enantiomer is also disclosed in US Patent No 4,943,590. Escitalopram has now been developed as an antidepressant. Hence, there is a desire for an improved method for preparation of escitalopram.

It is known to those skilled in the art that two enantiomers in certain situations may be separated by liquid chromatography using a chiral stationary phase. The chiral stationary phase has to be found by screening of the available chiral stationary phases for one, which is effective in separating the pair of enantiomers in question, and there may not always be an available chiral stationary phase suitable for the purpose.

Conventional liquid chromatography is a batch process consuming large amounts of solvents and, hence, is generally not economically feasible for industrial production. Chromatographic processes, which are advantageous by being continuous and generally consuming reduced amounts of solvents, are known to those skilled in the art. Simulated moving bed (SMB) chromatography is one such continuous chromatographic process.

EP 563,388 discloses a simulated moving bed (SMB) chromatographic process wherein enantiomers of an optically active compound are separated and the stationary phase comprises silica gel coated with a chiral material such as a cellulose ester.

Hence, there is a desire for a chiral stationary phase which is effective in separating the enantiomers of citalopram, or a compound which is an intermediate in the manufacture of citalopram.

There is no method which enables one, *a priori*, to forecast which chiral stationary phase will be effective in separating a given pair of enantiomers. The chiral stationary phase for separation of a pair of enantiomers has to be found by laborious testing of chiral stationary phases selected from the vast amount of available chiral stationary phases.

Objects of the Invention

One object of the invention is to provide a novel and economically feasible chromatographic method for separating the enantiomers of citalopram, or a compound which is an intermediate in the manufacture of citalopram.

Another object of the invention is to provide novel optically resolved intermediates for the manufacture of escitalopram.

Summary of the Invention

As used herein, the terms 'separation of enantiomers' and 'separation into enantiomers' refer to any process resulting in two or more fractions wherein the ratio between the two enantiomers deviates from 1:1. The term 'optically resolved' refers to the product of any such process.

As used herein, the term 'purity' means the purity of the enantiomer measured as percent enantiomeric excess (ee).

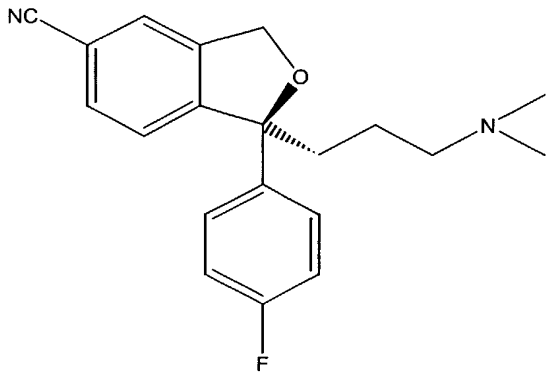
As used herein, the term 'carbohydrate derivative' means any compound which principally can be derived from a carbohydrate by substitution of one or more hydroxyl groups with another substituent leaving the stereochemical structure intact.

As used herein, the terms 'intermediate for the manufacture of escitalopram' and 'intermediate compounds in the preparation of citalopram' means any intermediate in any known process for the manufacture of escitalopram.

Throughout the application, structural formula of chiral compounds refer to the racemates if the stereochemistry is not indicated.

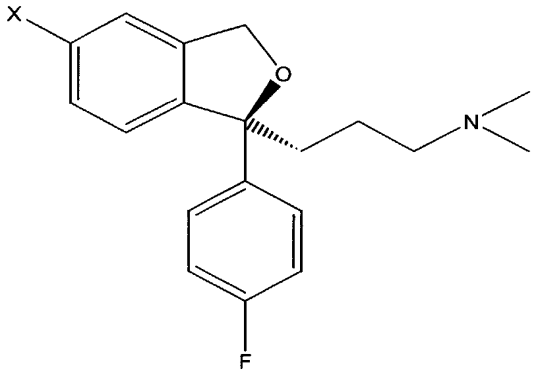
Laborious experimentation has now resulted in a new and inventive process for the manufacture of escitalopram comprising separation of the enantiomers of citalopram or an intermediate in the manufacture of citalopram by chromatography using a chiral stationary phase.

Accordingly, the present invention relates to a novel process for the preparation of escitalopram having the formula



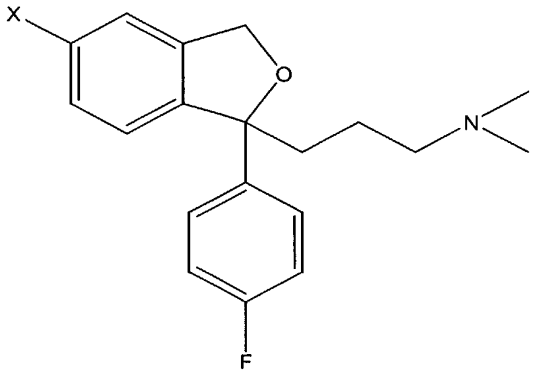
(III)

comprising preparation of a compound of formula



(IV)

wherein X is a cyano group, halogen or any other group which may be converted to a cyano group by optical resolution by chromatography of the racemic compound of formula

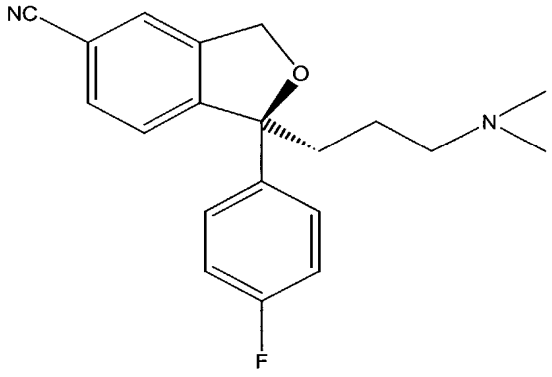


(V)

wherein X is as defined above; and if X is not a cyano group, then followed by conversion of X to a cyano group and thereafter isolation of escitalopram or a pharmaceutically acceptable salt thereof.

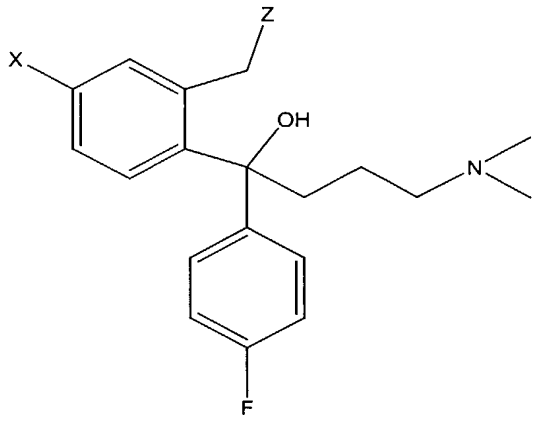
In one preferred embodiment of the invention, citalopram is separated into its enantiomers by chromatography using a chiral stationary phase.

Accordingly the present invention relates to a novel process for the preparation of escitalopram having the formula



(III)

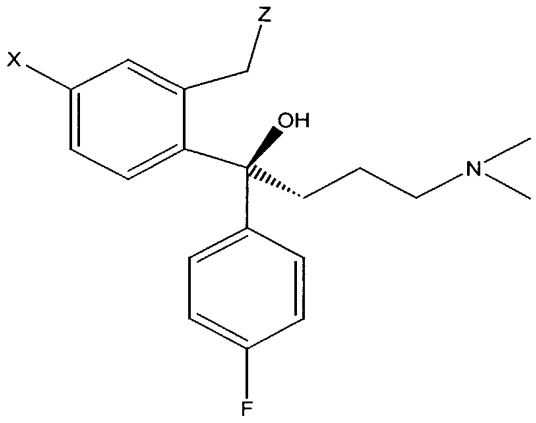
comprising optical resolution by chromatography of a compound of formula



(VI)

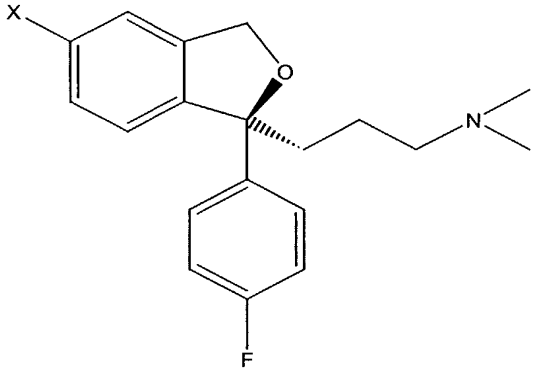
wherein X is a cyano group, halogen or any other group that may be converted to a

cyano group and Z is hydroxy or a leaving group, to form the compound of formula



(VII)

and if Z is OH conversion of the group Z to a leaving group and then ring closure of the resulting compound of formula (VII) wherein Z is a leaving group to form a compound of formula



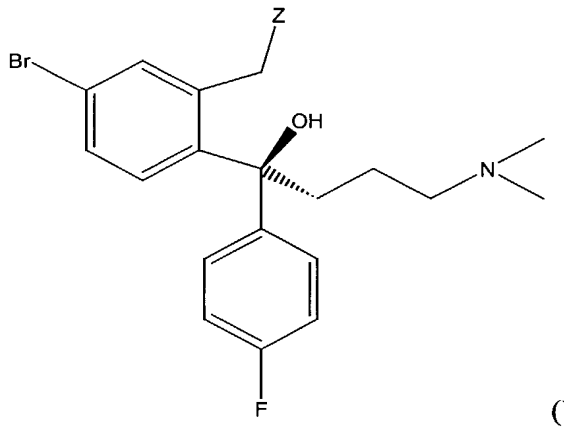
(IV)

wherein X is as defined above, and if X is not a cyano group, then followed by conversion of the group X in the compound of formula (III) to a cyano group, followed by isolation of escitalopram or a pharmaceutically acceptable salt thereof.

In another preferred embodiment of the invention, the intermediate diol II 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile is separated into its enantiomers by chromatography using a chiral stationary phase. The obtained (S)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile may be transformed into escitalopram by

methods known to those skilled in the art, such as treatment with para-toluensulfonylchloride and a base, e.g. triethylamine, as disclosed in US 4,943,590.

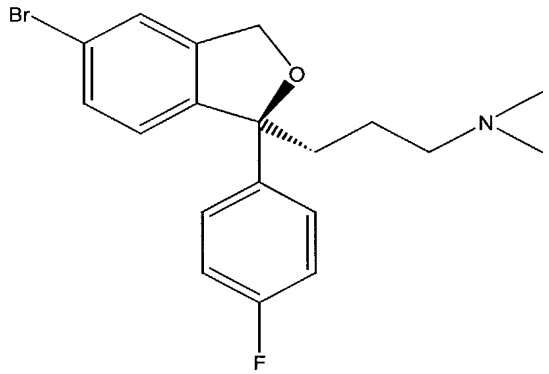
The invention also relates to the intermediate having the formula



(VIII)

wherein Z is as defined above.

In a further embodiment, the present invention relates to the S-enantiomer of 5-Br-citalopram having the formula



(IX)

or salts thereof.

The racemic compounds of formula (V) and (VI) may be resolved by liquid chromatography or super or sub critical chromatography using a chiral stationary phase.

The chiral stationary phase may comprise an optically active high molecular compound, e.g. a polysaccharide derivative, such as esters or carbamates of cellulose or amylose, a polyacrylate derivative (e.g. a methacrylate derivative, such as poly(triphenylmethylmethacrylate)) or a polyamide derivative, a protein with an asymmetric or disymmetric chain (bovine serum albumin bonded to silica, cellulase covalently bonded to aldehyde silica), polymers with an asymmetric centre in its side chains etc..

Another possibility is a chiral stationary phase comprising a low molecular compound having optical resolution capability, e.g. crown ethers ((S) or (R)-18-crown-6-ether on silica) and cyclodextrin derivatives (alpha cyclodextrin bonded to silica).

Other important chiral separation factors which may be comprised by the chiral stationary phase are amino acids and derivatives thereof, esters or amids of amino acids, acetylated amino acids and oligopeptides.

Still another possibility is a particulate polysaccharide material, e.g microcrystalline cellulose triacetate.

Chiral stationary phases including polysaccharide derivatives and polyamides useful for separation of enantiomers are described in EP 0 147 804, EP 0 155 637, EP 0 157 365, EP 0 238 044, WO 95/18833, WO 97/04011, EP 0656 333 and EP 718 625.

Particles of polysaccharides useful for the separation of optical enantiomers are described in EP 0706 982.

Preferably, the chiral stationary phase comprises a carbohydrate derivative, more preferred a polysaccharide derivative and most preferred an amylose or cellulose derivative.

Suitably, the polysaccharide adsorbed on the silica gel carry groups such as phenylcarbamoyl, 3,5-dimethyl-phenylcarbamoyl, 4-chlorophenylcarbamoyl, 3,5-

dichloro-phenylcarbamoyl, acetyl, benzoyl, cinnamoyl, 4-methyl-benzoyl or S-alpha-phenylethyl carbamoyl.

Preferably, the carbohydrate derivative comprises phenyl carbamate substituents, which optionally may be substituted with one or more C_{1-4}-alkyl groups, preferably methyl groups.

The chiral compound, which is the chiral separating factor of the stationary phase, may suitably be adsorbed on a carrier, such as silica gel.

Suitably, the chiral stationary phase is Chiralpak™ AD, a silica gel supported amylose derivative wherein the majority of the hydroxyl groups are substituted with 3,5-dimethylphenyl carbamate groups, or Chiralcel™ OD, a silica gel supported cellulose derivative wherein the majority of the hydroxyl groups are substituted with 3,5-dimethylphenyl carbamate groups. Chiralpak™ AD and Chiralcel™ OD are both obtainable from Daicel Chemical Industries Ltd.

Chiral stationary phases comprising amylose phenyl carbamate derivatives are especially suitable for resolvation of compounds of formula (VI). Exemplary of such chiral stationary phases is Chiralpak™ AD.

Chiral stationary phases comprising cellulose phenyl carbamate derivatives are especially suitable for resolvation of compounds of formula (V). Exemplary of such chiral stationary phases is Chiralcel™ OD.

The nature of the substituent X has little influence on the resolvation of the compounds as it is distant from the chiral center.

Any liquid chromatographic separation method may be used for the separation of the enantiomers. Preferably, the chromatographic separation method comprises a continuous chromatographic technology, suitably simulated moving bed technology.

The eluent is typically selected from the group comprising acetonitrile, alcohols, such as methanol, ethanol or isopropanol, and alkanes, such as cyclohexane, hexane or heptane, and mixtures thereof. An acid such as formic acid, acetic acid and trifluoroacetic acid and/or a base such as diethylamine, triethylamine, propylamine, isopropylamine and dimethyl-isopropyl-amine may be added to the eluent.

Alternatively, super or sub critical carbon dioxide containing a modifier may be used as eluent. The modifier is selected from lower alcohols such as methanol, ethanol, propanol and isopropanol. An amine, such as diethylamine, triethylamine, propylamine, isopropylamine and dimethyl-isopropyl-amine and optionally an acid, such as formic acid, acetic acid and trifluoroacetic acid may be added.

Suitably, the chromatographic method used is a liquid chromatographic method.

A suitable eluent according to this embodiment of the invention is acetonitrile.

Another suitable eluent according to this embodiment of the invention is a mixture of iso-hexane and isopropanol. A suitable mixture contains iso-hexane 98% vol and isopropanol 2% vol.

Another suitable eluent according to the invention is super or sub critical carbon dioxide containing 10% vol methanol with 0.5% vol diethylamine and 0.5% vol trifluoroacetic acid.

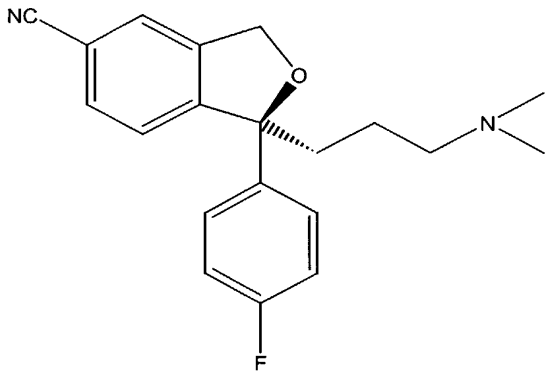
One embodiment of the invention comprises novel optically resolved intermediates for the manufacture of escitalopram.

When Z is OH in the compound of formula (VII), the alcohol group, Z, may be converted to a suitable leaving group such as a sulfonate ester or a halide. The former is carried out by reaction with sulfonyl halides, such as methanesulfonyl chloride and p-toluensulfonyl chloride. The latter is achieved by reaction with halogenating agents such as thionyl chloride or phosphorus tribromide.

Ring closure of the compounds of formula (VII), wherein Z is a leaving group, such as a sulfonate ester or halogen may thereafter be carried out by treatment with a base such as $KOC(CH_3)_3$ or other alkoxides, NaH or other hydrides, triethylamine, ethyldiisopropylamine or pyridine in an inert organic solvent, such as tetrahydrofuran, toluene, DMSO, DMF, t-butyl methyl ether, dimethoxyethane, dimethoxymethane, dioxane, acetonitrile or dichloromethane.

The ring closure is analogous to the process described in US 4,943,590.

The compound of formula (IV) may be converted to escitalopram having the formula



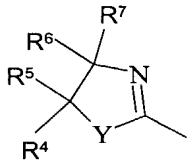
(III)

by a number of methods as described below.

As mentioned above, X in the compound of formula (IV) may be a cyano group, halogen, preferably chloro or bromo, or any other compound which may be converted to a cyano group.

Such other groups, X, which may be converted to a cyano group may be selected from the groups of formula CF_3-$(CF_2)_n$-SO_2-O- , wherein n is 0-8, -OH, -CHO, -CH_2OH, -CH_2NH_2, -CH_2NO_2, -CH_2Cl, -CH_2Br, -CH_3, -NHR^1, -$COOR^2$, -$CONR^2R^3$, wherein R^1 is hydrogen or alkylcarbonyl, and R^2 and R^3 are selected from hydrogen optionally substituted alkyl, aralkyl or aryl ,

and a group of formula



(X)

wherein Y is O or S;

R^4 – R^5 are each independently selected from hydrogen and C_{1-6} alkyl or R^4 and R^5 together form a C_{2-5} alkylene chain thereby forming a spiro ring; R^6 is selected from hydrogen and C_{1-6} alkyl, R^7 is selected from hydrogen, C_{1-6} alkyl, a carboxy group or a precursor group for a carboxy group, or R^6 and R^7 together form a C_{2-5} alkylene chain thereby forming a spiro ring.

When X is halogen, in particular bromo or chloro, conversion of the compound of formula (IV) to form escitalopram may be carried out according to the procedures described in US 4,136,193, WO 00/13648, WO 00/11926 and WO 01/02383 or other procedures suitable for such conversions.

According to US 4,136,193, conversion of the 5-bromo group may be carried out by reaction of a compound of formula (IV) wherein X is bromo, with CuCN.

WO 00/13648 and WO 00/11926 describes the conversion of a 5-halogen or a triflate group to a cyano group by cyanation with a cyanide source in presence of a Pd or Ni catalyst.

The cyanide source used according to the catalysed cyanide exchange reaction may be any useful source. Preferred sources are KCN, NaCN or $(R')_4NCN$, where $(R')_4$ indicates four groups which may be the same of different and are selected from hydrogen and straight chain or branched C_{1-6} alkyl.

The cyanide source is used in stoichiometric amount or in excess, preferably 1-2 equivalents are used pr. equivalent starting material. $(R')_4N^+$ may conveniently be $(Bu)_4N^+$. The cyanide source is preferably NaCN or KCN or $Zn(CN)_2$.

The palladium catalyst may be any suitable Pd(0) or Pd(II) containing catalyst, such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(PPh)_2Cl_2$, etc. The Pd catalyst is conveniently used in an amount of 1-10, preferably 2-6, most preferably about 4-5 mol%.

In one embodiment, the reaction is carried out in the presence of a catalytic amount of Cu^+ or Zn^{2+}. Catalytic amounts of Cu^+ and Zn^{2+}, respectively, means substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 mol. Conveniently, about ½ eq. is used per eq. Pd. Any convenient source of Cu^+ and Zn^{++} may be used. Cu^+ is preferably used in the form of CuI, and Zn^{2+} is conveniently used as the $Zn(CN)_2$ salt.

In a preferred embodiment, cyanation is carried out by reaction with $ZnCN_2$ in the presence of a Palladium catalyst, preferably $Pd(PPh_3)_4$ (tetrakis(triphenylphosphine)palladium).

The nickel catalyst may be any suitable Ni(0) or Ni(II) containing complex which acts as a catalyst, such as $Ni(PPh_3)_3$, (σ-aryl)-$Ni(PPh_3)_2Cl$, etc. The nickel catalysts and their preparation are described in WO 96/11906, EP-A-613720 and EP-A-384392.

In a particularly preferred embodiment, the nickel(0) complex is prepared *in situ* before the cyanation reaction by reduction of a nickel(II) precursor such as $NiCl_2$ or $NiBr_2$ by a metal, such as zinc, magnesium or manganese in the presence of excess of complex ligands, preferably triphenylphosphin.

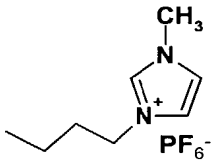
The Ni-catalyst is conveniently used in an amount of 0.5-10, preferably 2-6, most preferably about 4-5 mol%.

In one embodiment, the reaction is carried out in the presence of a catalytic amount of Cu^+ or Zn^{2+}.

Catalytic amounts of Cu^+ and Zn^{2+}, respectively, means substoichiometric amounts such as 0.1 - 5, preferably 1 - 3%. Any convenient source of Cu^+ and Zn^{2+} may be used. Cu^+ is preferably used in the form of CuI and Zn^{2+} is conveniently used as the $Zn(CN)_2$ salt or formed *in situ* by reduction of a nickel (II) compounds using zinc.

The cyanation reaction may be performed neat or in any convenient solvent, such solvent includes DMF, NMP, acetonitril, propionitrile, THF and ethylacetate.

The cyanide exchange reaction may also be performed in an ionic liquid of the general formula $(R'')_4N^+$, Y^-, wherein R'' are alkyl-groups or two of the R'' groups together form a ring and Y^- is the counterion. In one embodiment of the invention, $(R'')_4N^+Y^-$ represents



In still another alternative, the cyanide exchange reaction is conducted with apolar solvents such as benzene, xylene or mesitylene and under the influence of microwaves by using *i.e.* Synthewave 1000™ by Prolabo.

The temperature ranges are dependent upon the reaction type. If no catalyst is present, preferred temperatures are in the range of 100-200 °C. When the reaction is conducted under the influence of microwaves, the temperature in the reaction mixture may raise to above 300 °C. More preferred temperature ranges are between 120-170 °C. The most preferred range is 130-150 °C.

If a catalyst is present, the preferred temperature range is between 0 and 100 °C. More preferred are temperature ranges of 40-90 °C. Most preferred temperature ranges are between 60-90 °C.

Other reaction conditions, solvents, etc. are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

Another process for the conversion of a compound of formula (IV), wherein X is Br to the corresponding 5-cyano derivative involves reaction of 5 -Br-citalopram of formula (IV) with magnesium to form a Grignard reagent, followed by reaction with a formamide to form an aldehyde. The aldehyde is converted to an oxime or a hydrazone which is converted to a cyano group by dehydration and oxidation, respectively.

Alternatively, 5-Br-citalopram of formula (IV), wherein X is bromo, may be reacted with magnesium to form a Grignard reagent, followed by reaction with a compound containing a CN group bound to a leaving group.

A detailed description of the above two procedures may be found in WO 01/02383.

Compounds of formula (IV), wherein the group X is –CHO, may be converted to escitalopram by methods analogous to those described in WO 99/30548.

Compounds of formula (IV), wherein the group X is NHR^1, wherein R^1 is hydrogen or alkylcarbonyl may be converted by to escitalopram methods analogous to those described in WO 98/19512.

Compounds of formula (IV), wherein the group X is $-CONR^2R^3$, wherein R^2 and R^3 are selected from hydrogen optionally substituted alkyl, aralkyl or aryl, may be converted to escitalopram by methods analogous to those described in WO 98/19513 and WO 98/19511.

Compounds of formula (IV), wherein the group X is a group of formula (X), may be converted to escitalopram by methods analogous to those described in WO 00/23431.

Compounds of formula (IV), wherein X is OH, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NO_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_3$ and any of the other groups X above, may be converted to escitalopram by methods analogous to those prepared in WO 01/168632.

Starting materials of formulas (V) and (VI) may be prepared according to the above mentioned patents and patent applications or by analogous methods.

Thus the acid addition salts used according to the invention may be obtained by treatment of intermediates for the synthesis of escitalopram with the acid in a solvent followed by precipitation, isolation and optionally re-crystallisation by known methods and, if desired, micronisation of the crystalline product by wet or dry milling or another convenient process or preparation of particles from a solvent-emulsification process.

In the following, the invention is illustrated by way of examples. However, the examples are merely intended to illustrate the invention and should not be construed as limiting.

Example 1

Separation of the enantiomers of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile

4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile, which may be manufactured according to US patent No 4,650,884, was separated into its enantiomers as follows.

A Novasep Licosep™ 10-50 Simulated Moving Bed Chromatograph was fitted with eight 50 mm i.d. columns each packed to a bed length of 15 cm with Chiralpak™ AD (20 μm) packing material using standard techniques. A SMB system of 8 columns in a 2-2-2-2 configuration was chosen for this separation. Acetonitrile (Baker HPLC grade) was used as mobile phase.

The SMB operating conditions were:

Temperature:	30 °C
Feed Flow (65 mg/mL):	10 mL/min
Eluent Flow (make-up):	102 mL/min
Extract Flow:	69 mL/min
Raffinate Flow:	48 mL/min
Recycle Flow:	210 mL/min
Switch Time:	1.18 min

The products were isolated from the eluent by evaporation resulting in viscous oils. Both enantiomers were isolated with a purity exceeding 99% ee.

The obtained (S)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile may be transformed into escitalopram by methods known to those skilled in the art, such as treatment with para-toluensulfonylchloride and a base, e.g. triethylamine, as disclosed in US 4,943,590.

Example 2

Separation of 1-(4-bromo-2-hydroxymethyl-phenyl)-4-dimethylamino-1-(4-fluorophenyl)-butan-1-ol.

A column with the dimensions 280 x 110 mm packed with ChiralPak® (20 μm particle size) was used as the chiral stationary phase. A mixture of 95% acetonitrile and 5% methanol was used as the mobile phase.

The operation conditions were as follows:

Temperature: 29 °C
Flow rate: 500 mL/min
Detection: UV 280 nm

500 g of a crude citalopram product containing 89% racemate was separated on the column. The first eluting enantiomer with a retention time of 11.0 min was isolated from the eluent with an enantiomeric excess of 99.5% in 99% yield. The second

eluting enantiomer with a retention time of 14.1 min was isolated from the eluent with an enantiomeric excess of 99.2% in 98% yield.

Example 3

Separation of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophtalane into its enantiomers.

A column with the dimensions 280 x 110 mm packed with Chiralcel®OD (20 µm particle size) was used as the chiral stationary phase. A mixture of 98% vol isohexane and 2% vol isopropanol was used as the mobile phase.

The operation conditions were as follows:

Temperature: Ambient temperature
Flow rate: 500 mL/min
Detection: UV 285 nm

500 g of a crude product containing 89% racemate was separated on the column. The first eluting enantiomer with a retention time of 5.4 min was isolated from the eluent with an enantiomeric excess of 99.5% in 96% yield. $[\alpha]_D = -0.81°$ (c = 0.99, MeOH); The second eluting enantiomer with a retention time of 6.7 min was isolated from the eluent with an enantiomeric excess of 99.4% in 99% yield. $[\alpha]_D = +0.95°$ (c = 1.26, MeOH);

Example 4

Separation of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophtalane into its enantiomers using supercritical fluid chromatography.

A column with the dimensions 250 x 10 mm packed with Chiralcel®OD (10 µm particle size) was used as the chiral stationary phase. As mobile phase was used carbon dioxide and modifier in a ratio of 90:10. The modifier was methanol with diethylamine (0.5%) and trifluoroacetic acid (0.5%).

The operation conditions were as follows:

Temperature: Ambient temperature
Flow rate: 18.9 mL/min
Pressure: 20 kPa
Detection: UV 254 nm

75 mg of racemic mixture was separated on the column.
Both enantiomers were isolated from the eluent. The enantiomers were isolated with an enatiomeric excess of 86.1% (RT 3.25 min) and 87.1% (RT 3.67 min), respectively.

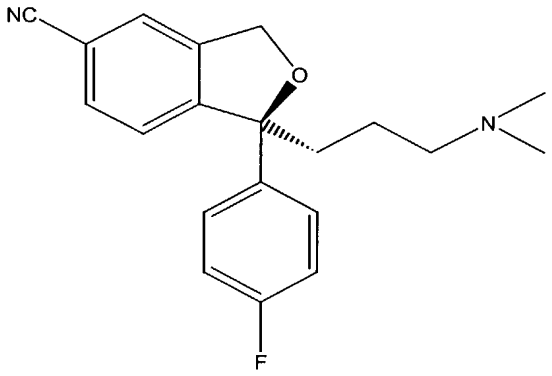
Example 5

Cyanation of (+)-1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophtalane.

5.0 g of the (+)- enantiomer was treated with 3.1 g of $Zn(CN)_2$ and 0.76 g of $Pd(PPh_3)_4$ under the conditions described in the WO 00/13648. The enantiomeric purity of the product was analysed by chiral electrophoresis. Based on the results from chiral electrophoresis and supercritical fluid chromatography, the product was shown to be identical with escitalopram. Yield: 80%; ee 99.6%

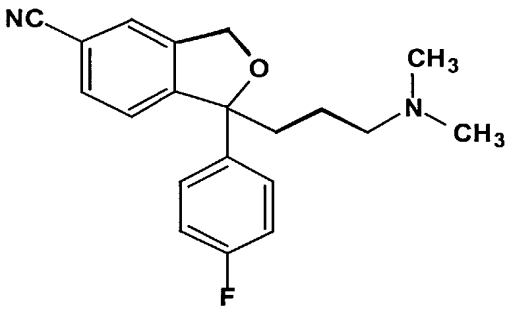
Claims

1. Method for preparation of escitalopram having the formula



(III)

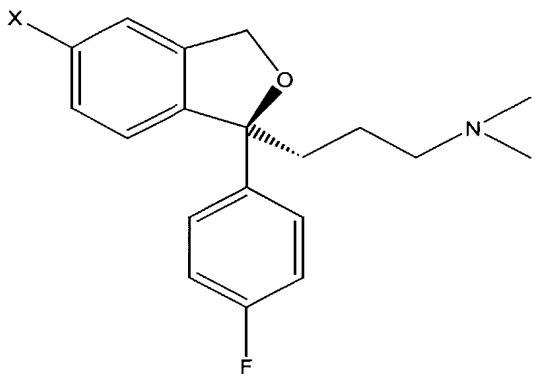
or pharmaceutically acceptable addition salts thereof comprising separation of the enantiomers of a compound selected from the group comprising citalopram having the formula



(I)

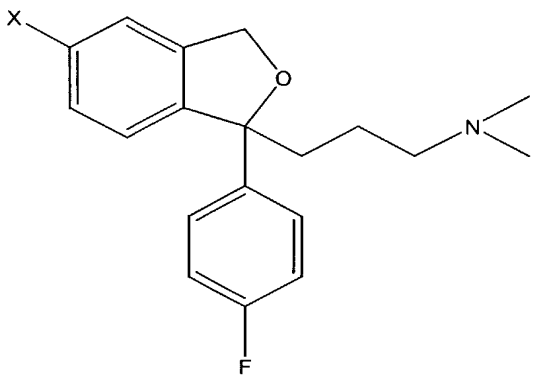
and intermediate compounds in the preparation of citalopram, **characterised in that** said separation of enantiomers is performed by liquid chromatographic separation of enantiomers using a chiral stationary phase for the chromatography.

2. A method according to claim 1 comprising preparation of a compound of formula



(IV)

wherein X is a cyano group or halogen or any other group that may be converted to a cyano group, by optical resolution by chromatography of a racemic compound of formula



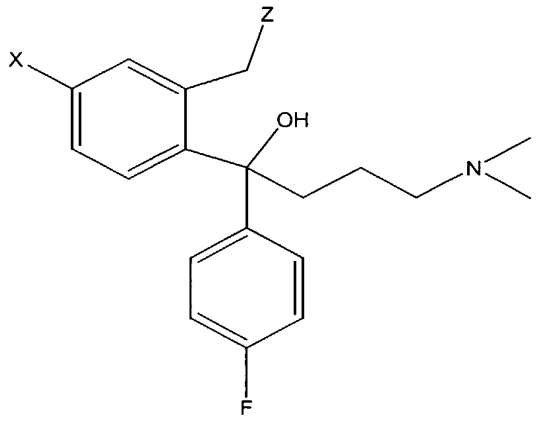
(V)

wherein X is as defined above, and if X is not a cyano group then followed by conversion of the group X in the compound of formula (IV) to a cyano group followed by isolation of escitalopram or a pharmaceutically acceptable salt thereof.

3. Method according to claim 2, wherein the group X is cyano.

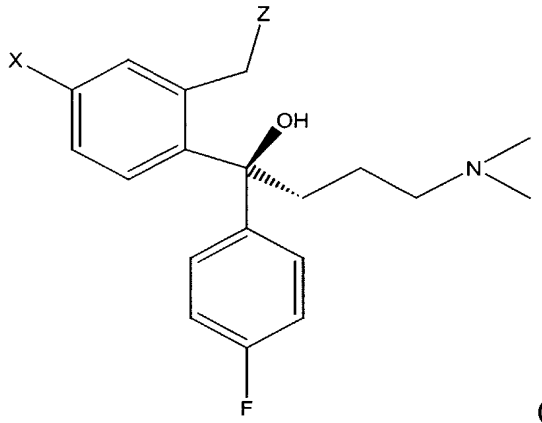
4. The method according to claim 2, wherein the group X is bromo.

5. A method according to claim 1 comprising optical resolution by chromatography of a compound of formula



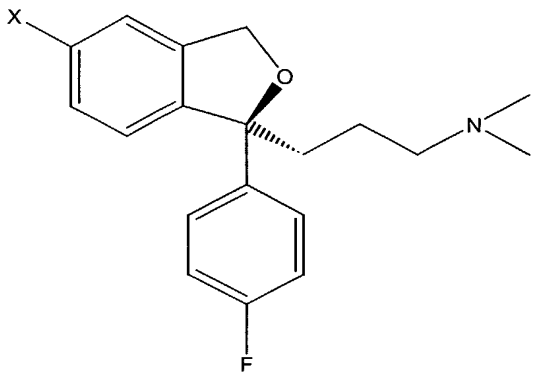
(VI)

wherein X is a cyano group or halogen or any other group that may be converted to a cyano group and Z is hydroxy or a leaving group, to form the compound of formula



(VII)

and if Z is OH conversion of the group Z to a leaving group and then ring closure of the resulting compound of formula (VII) wherein Z is a leaving group to form a compound of formula



(IV)

wherein X is as defined above, and if X is not a cyano group then conversion of the group X in the compound of formula (IV) to a cyano group, followed by isolation of escitalopram or a pharmaceutically acceptable salt thereof.

6. Method according to claim 5, wherein the group X is cyano.

7. Method according to claim 5, wherein the group X is bromo.

8. Method according to any of claims 1-7, **characterised in that** the chiral stationary phase comprises a carbohydrate derivative.

9. Method according to claim 8, **characterised in that** the carbohydrate derivative is a polysaccharide derivative.

10. Method according to any of claims 8-9, **characterised in that** the carbohydrate derivative comprises phenyl carbamate substituents which optionally may be substituted with one or more C_{1-4}-alkyl groups, preferably methyl groups.

11. Method according to any of claims 9-10, **characterised in that** the polysaccharide derivative is an amylose derivative.

12. Method according to claim 11, **characterised in that** the chiral stationary phase comprising an amylose derivative comprising optionally alkyl substituted phenyl carbamate substituents is Chiralpak™ AD from Daicel Chemical Industries Ltd.

13. Method according to any of claims 9-10, **characterised in that** the polysaccharide derivative is a cellulose derivative.

14. Method according to claim 13, **characterised in that** the chiral stationary phase comprising a cellulose derivative comprising optionally alkyl substituted phenyl carbamate substituents is Chiralcel™ OD from Daicel Chemical Industries Ltd.

15. Method according to any of claims 8-14, **characterised in that** the carbohydrate derivative is adsorbed on silica gel.

16. Method according to any of claims 1-15, **characterised in that** the chromatographic separation comprises a continuous chromatographic process, suitably Simulated Moving Bed technology.

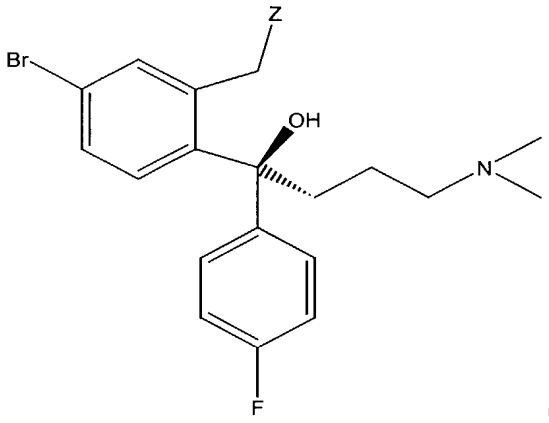
17. The method according to any of claims 1-16 wherein a compound of formula (III), wherein X is halogen, in particular bromo, is converted to escitalopram by reaction of the compound of formula (IV) with CuCN followed by purification and isolation of escitalopram or a pharmaceutically acceptable salt thereof.

18. The method according to any of claims 1-16, wherein the compound of formula (IV), wherein X is halogen, in particular bromo, or CF_3-$(CF_2)_n$-SO_2-O-, wherein n is 0-8, is converted to escitalopram by reaction of the compound of formula (III) with a cyanide source in presence of a palladium catalyst followed by purification and isolation of escitalopram or a pharmaceutically acceptable salt thereof.

19. The method according to any of claims 1-16 wherein a compound of formula (IV) wherein X is halogen, in particular bromo, is converted to escitalopram by reaction of a compound of formula (III) with a cyanide source in presence of a nickel catalyst

followed by purification and isolation of escitalopram or a pharmaceutically acceptable salt thereof.

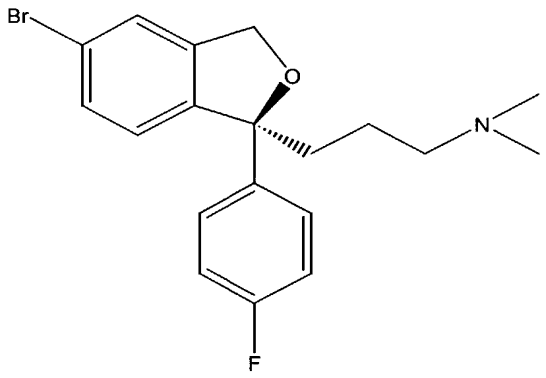
20. An intermediate having the formula



(VIII)

wherein Z is as defined in claim 1; or a salt thereof.

21. An intermediate having the formula



(IX)

or a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00491

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87, C07B 57/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Chromatography B, Volume 685, 1996, Dan Haupt: "Determination of citalopram enantiomers in human plasma by liquid chromatographic separation on a Chiral-AGP column", page 299 - page 305 --	1-19
X	Chromatographia. An International Journal for Rapid Communication in Chromatography, Electrophoresis, and Associated Techniques, Volume 53, March 2001, B. Carlsson et al: "Optimization and Characterization of the Chiral Separation of Citalopram and its Demethylated Metabolites by Response-Surface Methodology", abstract 266, retrieved on 2002-10-28 http://www.chromatographia.de/chroma/daten/march_53_abstracts.htm --	1-19

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 December 2002	05 -12- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00491

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0143525 A2 (H. LUNDBECK A/S), 21 June 2001 (21.06.01), page 11 - line 19	1-19
	--	
X	ChromTech, "Separation of enantiomers by chiral chromatography/chiral HPL", retrieved on 2002-10-29, http://www.chromtech.se/	1-19
	--	
A	US 4943590 A (BOEGESOE ET AL), 24 July 1990 (24.07.90)	20-21
	--	
A	US 4136193 A (BOGESO ET AL), 23 January 1979 (23.01.79)	20-21
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00491

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-21

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

As is stated in Annex B to Administrative Instructions under the PCT, in force July 1, 1998, (PCT GAZETTE 1998, June 25, pp 45-50) unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features"- i.e. features that define a contribution which each of the inventions makes over the prior art (cf. PCT Rule 13.2). It is well known to a person skilled in the art, that compounds with 5-HT4 receptor agonist activity have pharmaceutical use. This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

Invention 1. A process according to claims 1-19 concerning a method of preparation of escitalopram by liquid chromatography.

Invention 2. An intermediate compound VII according to claim 20.

Invention 3. An intermediate compound IX according to claim 21.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/02

International application No.
PCT/DK 02/00491

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0143525 A2	21/06/01	AU 3535701 A	03/09/01
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		BE 1012921 A	08/05/01
		FR 2805812 A	07/09/01
		FR 2805813 A	07/09/01
		GR 2001100097 A	31/10/01
		GR 2001100098 A	31/10/01
		NL 1017414 C	00/00/00
		NL 1017415 C	00/00/00
		US 6420574 B	16/07/02
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		HU 9500496 A	28/09/95
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		PT 90845 A,B	29/12/89
		US RE34712 E	30/08/94
		ZA 8904476 A	25/04/90

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/02

International application No.
PCT/DK 02/00491

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AT 360001 B	10/12/80
		AT 360002 B	10/12/80
		AT 571979 A	15/05/80
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		IE 44055 B,L	29/07/81
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